

Prevention of food allergy

Ashley L. Devonshire, M.D., MPH and Rachel Glick Robison, M.D.

ABSTRACT

Primary prevention and secondary prevention in the context of food allergy refer to prevention of the development of sensitization (i.e., the presence of food-specific immunoglobulin E (IgE) as measured by skin-prick testing and/or laboratory testing) and sensitization plus the clinical manifestations of food allergy, respectively. Until recently, interventions that target the prevention of food allergy have been limited. Although exclusive breast-feeding for the first 6 months of life has been a long-standing recommendation due to associated health benefits, recommendations regarding complementary feeding in infancy have significantly changed over the past 20 years. There now is evidence to support early introduction of peanut into the diet of infants with egg allergy, severe atopic dermatitis, or both diagnoses, defined as high risk for peanut allergy, to try to prevent development of peanut allergy. Although guideline-based recommendations are not available for early introduction of additional allergenic foods, this topic is being actively studied. There is no evidence to support additional dietary modification of the maternal or infant diet for the prevention of food allergy. Similarly, there is no conclusive evidence to support maternal avoidance diets for the prevention of food allergy.

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In recent years, with the publication of a few landmark studies in food allergy,^{1,2,3} attention has expanded from food allergy diagnostics and therapeutics to include prevention. Primary prevention and secondary prevention in the context of food allergy refer to prevention of sensitization (i.e., the presence of food-specific immunoglobulin E as measured by skin-prick testing and/or laboratory testing) or sensitization plus the clinical manifestations of food allergy. New guidelines for prevention of food allergy are in stark contrast to long-standing recommendations by pediatricians and primary care providers with regard to food introduction practices early in life and have shifted the conversation toward prevention.⁴

MATERNAL DIET, BREAST-FEEDING, AND PREVENTION

The American Academy of Pediatrics; the American Academy of Allergy, Asthma & Immunology; the American College of Allergy, Asthma & Immunology; and the European Academy of Allergy and Clinical Immunology all recommend exclusive breast-feeding of infants until approximately 6 months of age.^{5,6,7} Breast-feeding is beneficial for both the infant and the mother, and has been associated with multiple positive health outcomes. In the instance when exclusive

breast-feeding is not possible and the infant has an immediate family history of atopy, the use of a partially or extensively hydrolyzed infant formula should be considered for the prevention of atopic dermatitis and cow's milk allergy.^{5,8} This recommendation is supported by the European Academy of Allergy and Clinical Immunology; the American College of Allergy, Asthma & Immunology; and the American Academy of Allergy, Asthma & Immunology.

It is known that allergenic protein is excreted into breast milk in variable quantities and with variable timing relative to maternal ingestion. Currently, there is no evidence to support the role of maternal avoidance diets or supplementation of the maternal diet during pregnancy or lactation for the prevention of food allergy.^{5,8}

EARLY ALLERGENIC FOOD INTRODUCTION

Historically, professional societies have supported the delayed introduction of highly allergenic foods; however, more recently, evidence is accumulating to support the early introduction of allergenic foods. The Learning Early About Peanut Allergy trial,¹ published in the *New England Journal of Medicine* in February 2015, was an open-label, randomized controlled trial of early peanut introduction among infants (with diagnosed egg allergy and/or severe eczema) 4–11 months of age and at high risk. Infants at high risk underwent peanut skin-prick testing, and, if the peanut skin-prick test wheal size was 0–4 mm, then the infants were randomized to strict peanut avoidance versus regular peanut consumption until 5 years of age, at which point, peanut oral food challenges were conducted. The findings were dramatic and showed a marked reduction in the prevalence of peanut allergy from 17.2% in the avoid-

From the Division of Allergy and Immunology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois

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Address correspondence to Rachel G Robison, M.D., Box 60, 225 East Chicago Ave Chicago, IL 60611

E-mail address: rrobison@luriechildrens.org

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ance group to 3.2% in the early consumption group.¹ The study investigators then sought to determine if this protective effect of early peanut consumption would persist, despite 12 months of peanut avoidance. The Persistence of Oral Tolerance to Peanut (LEAP-On) study² results showed that the reduction in the prevalence of peanut allergy seen with early peanut consumption persisted despite 12 months of complete peanut avoidance.

These findings prompted the generation and publication of the 2017 National Institute of Allergy and Infectious Diseases sponsored “Addendum guidelines for the prevention of peanut allergy in the United States.”⁴ The guidelines establish recommendations for peanut introduction for three groups of infants, those with (1) severe eczema, egg allergy, or both; (2) mild-to-moderate eczema; and (3) no eczema or any food allergy.⁴ Infants with severe eczema and/or egg allergy should be evaluated for evidence of peanut sensitization by using skin-prick testing or specific-immunoglobulin E measurement before decision-making with regard to peanut introduction, which should occur by 4–6 months of age.⁴ Age-appropriate peanut-containing foods should be introduced to infants with mild-to-moderate eczema at 6 months of age, and, in infants without any history of atopy (*i.e.*, eczema or food allergy), these foods can be introduced at any time, based on family preference.⁴

To address the question of whether the protective effect of early peanut introduction would translate to other highly allergenic foods, the Enquiring About Tolerance trial³ randomized 3-month-old infants who were exclusively breast-fed from the general population to early versus regular timed introduction of common allergenic foods (peanut, boiled egg, cow’s milk, sesame, fish, and wheat). In this study, when the analysis was limited to only those families that strictly complied with the intervention, it showed a 67% reduction in the risk of food allergy in the early introduction group, particularly for egg and peanut allergy.³ The results of additional studies that evaluated early introduction of other allergenic foods are variable. The Starting Time of Egg Protein trial,⁹ a double-blind, randomized controlled trial of raw whole egg powder introduction among 4–6-month-old infants of mothers with allergy, found no difference in challenge-proven egg allergy between infants in the early egg introduction group versus placebo (7% versus 10.3%) at 1 year of age.

In contrast, the Prevention of Egg Allergy with Tiny Amount Intake study¹⁰ was a randomized, double-blind, placebo controlled trial of heated egg powder introduction among 4–5-month-old infants with atopic dermatitis. At interim analysis, 9% of infants in the early egg introduction group compared with 38% of infants in the placebo group had challenge-proven egg

allergy at 1 year of age, which resulted in early termination of the study.¹⁰ A large meta-analysis that examined the literature on complementary infant feeding and the risk of allergic disease found that early introduction of egg and peanut is associated with a decreased risk of egg and peanut allergy separately.¹¹ It is important to note that the number of studies that evaluated the effect of early introduction remains few. Therefore, the only current guidelines published in the United States that recommend early allergenic food introduction pertain to peanut introduction in a high-risk patient population (*i.e.*, known egg allergy, severe atopic dermatitis, or both diagnoses). It is also important to emphasize that some infants may already have clinical peanut allergy before attempted early peanut introduction, as was seen in 2.2% of infants randomized to the early peanut introduction group in the Learning Early About Peanut Allergy trial.¹

FUTURE DIRECTIONS AND UNANSWERED QUESTIONS

Although the Enquiring About Tolerance study³ investigated the effect of early introduction of multiple allergenic foods, it was difficult for a number of families to comply with the intervention. As such, the effect of early introduction of other highly allergenic foods is unknown. There remains a need for additional studies that assess the effect of early introduction of other highly allergenic foods into the infant diet.

As discoveries regarding the underlying pathophysiology of sensitization and clinical food allergy have been made, the dual-allergen exposure hypothesis has been generated. Briefly, this hypothesis suggests that tolerance to allergen develops through oral exposure; however, exposure to an allergen through a defective skin barrier can also promote sensitization and development of food allergy.¹² With this in mind and awareness of the atopic march, there is a question as to whether targeting the development of atopic dermatitis may prevent the development of food allergy. Studies that investigate this strategy are ongoing.

There also is a question as to whether particular dietary interventions (*e.g.*, probiotics, prebiotics, vitamin D) may prevent or modulate the development of allergic disease. At this time, supplementation of the diet with prebiotics or probiotics during pregnancy or early infancy is currently not recommended due to a lack of evidence of their efficacy in primary prevention of atopy.⁸ There are multiple studies currently underway to investigate further strategies for the primary and secondary prevention of food allergy.

IMMUNOLOGY

- The dual allergen exposure hypothesis suggests that oral exposure to food allergen promotes the

development of tolerance through Th1 and regulatory T-cell populations. Exposure to food allergen through a disrupted skin barrier leads to sensitization through Th2 skewing and allergic cytokine production.

CLINICAL PEARLS

- When presented with an infant with a known egg allergy, severe atopic dermatitis or both diagnoses providers should strongly consider evaluation for sensitization to peanut before introduction, which should occur at approximately 4–6 months of age.
- There currently are no guidelines with regard to early introduction of other highly allergenic foods for the prevention of food allergy.
- At this time, no modifications are advised to the maternal diet during pregnancy or lactation as a means for prevention of food allergy.

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